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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Cistus creticus* L., herba

Draft

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Cistus creticus* L., herba (pink rock-rose)
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Cistus creticus* L., herba. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

There is no monograph for *Cistus,* neither in European Pharmacopoeia nor in any other national Pharmacopoeias or Codexes.

Cistus L. or rock rose, is a genus of perennial herbaceous plants that have hard leaves and grow in open areas of stony and infertile soils. They are indigenous to the Mediterranean region. The genus is currently thought to comprise approximately 20 species, of which 16 occur in Europe.

C. creticus is a small, woody, seasonally dimorphic plant, distributed along the coast of the Central-Eastern Mediterranean (except France and the Iberian Peninsula), Northern Africa, Western Asia and Brazil (Blaschek et al. 2014). It extends from sea level to 800 m in arid and warm areas of chaparral and garrigue, has five violet petals on its bisexual flowers (rock rose), numerous stamens, the fruit a capsule and the seeds small, with hard water-impermeable coating (Papaefthimiou *et al*. 2014).

Cistus creticus L. (Cistaceae), is given with several subspecies (Lukas *et al.* 2021):
Cistus creticus subsp. *creticus* Greuter & Burdet
Cistus creticus subsp. *eriocephalus* (Viv.) Greuter & Burdet , and
Cistus creticus subsp. *corsicus* (Loisel.) Greuter & Burdet and (recently)
Cistus creticus subsp. *trabutii* (Maire) Dobignard (worldfloraonline)

C. creticus is synonym with:

Cistus creticus f. *albus* (O.E.Warb.) Demoly, *Cistus creticus* f. *flavus* (O.E.Warb.) Demoly, *Cistus creticus* f. *flavus* (O.E.Warb.) Demoly, *Cistus creticus* f. *flavus* (O.E.Warb.) Demoly, *Cistus creticus* f. *flavus* Demoly, *Cistus villosus* f. *albus* O.E.Warb., *Cistus complicates,* Spruner ex Nyman, *Cistus corsicus* Loisel *Cistus cupanianus* C.Presl, *Cistus dunalianus* Sweet, *Cistus garganicus* Ten.. *Cistus incanus* subsp. *Creticus* (L.) Heywood, *Cistus ladaniferus* Stokes, *Cistus philothei* Sennen & Mauricio, *Cistus polymorphus* Willk. *Cistus rotundifolius* Sweet, *Cistus tomentosus* Lam., *Cistus undulatus* Moench, *Cistus villosus* L., *Cistus villosus* var. *creticus* (L.) Boiss. *Cistus villosus* var. *rotundifolius,* (Sweet) Grosser, *Cistus villosus* var. *undulatus* Grosser, *Cistus vulgaris* Spach (worldfloraonline searched 29 sept 2023)

- **Chemical constituents**

In *C. creticus* subsp. *creticus* several terpenes (monoterpenes, sesquiterpenes, and labdane-type diterpenes) and phenyl propanoids-flavonoids have been reported (Zaleg *et al.* 2021).

In *C. creticus* subsp. *eriocephalus* several terpenes (consisting also of monoterpenes, sesquiterpenes, and labdane-type diterpenes) and some carbonylic compounds have been detected (Zaleg *et al*. 2021; Tomou *et al.* 2022)

Terpenoids (labdane diterpenes)
The labdane derivatives labd-13(E)-ene,8a-15-diol, labd-7,13-(E)-dien-15-ol, labd-13(E)-en-8a-ol-15-yl acetate, labd-7,13(E)-dien-15-yl acetate and an ent-manoyl oxide mixture of the isomers (ent-13-epi-manoyl oxide; ent-manoyl oxide; ent-8-epi-manoyl oxide) were identified and characterised from hexane extracts and of the essential oils of the leaves, fruits and resin of *C. creticus* (=ladano) (Demetzos *et al*., 1990).

Polyphenols, catechins:
air-dried aerial plant parts: catechin, gallocatechin, protocatechuic acid, shikimic acid, and gallocatechin-3-gallate, as well as dimeric and trimeric derivatives, epigallocatechin-(4β→8)-catechin

and epigallocatechin-(4β→8)- gallocatechin, structurally related galloylated isomers, epigallocatechin-3-Ogallate-(4β→8)-gallocatechin, epigallocatechin-3-O-gallate-(4β→6)-gallocatechin, gallocatechin-(4α→8)-gallocatechin-(4α → 8)-gallocatechin (Demetzos *et al*., 1990; Danne *et al*., 1993; Petereit *et al*., 1991).

leaves: polyphenols, especially flavonoids (glycosides of flavonols) and tannins (proanthocyanidins and ellagitannins). Derivatives of flavonols and flavan-3-ols as well: kaempferol 3-O-beta-glucopyranoside, quercetin 3-O-beta-D-glucopyranoside, quercetin 3-O-beta-D-rutinoside, myricetin 3-O-α-L-rhamnopyranoside, myricetin 3-O-beta-D-galactopyranoside, coumarin aesculin (Demetzos *et al*., 1990); flavonoid derivatives from kaempferol, quercetin, apiginin and naringenin, scopoletin (6-O-methyl-7-hydroxycoumarin) (Demetzos *et al*., 1990; Danne *et al*., 1993; Petereit *et al*., 1991). Two proanthocyanidin trimers have been isolated from *Cistus incanus* herb; gallocatechin-(4α→6)-gallocatechin-(4α→8)-gallocatechin and epigallocatechin-3-O-gallate-(4ß→8)-epigallocatechin-3-O-gallate-(4ß→8)-gallocatechin. A more abundant proanthocyanidin oligomer was also isolated. The mean molecular weight of the polymer was estimated to be about 7 to 8 flavan-3-ol-units with a ratio of procyanidin : prodelphinidin units at 1:5, some of which are derivatised by gallic acid. (Mansoor et al. 2016). Recently, a new ellagitannin cistusin together with well-known terflavin A and punicalagin were isolated and determined by spectroscopic evidence (Fecka *et al*. 2020).

- Herbal preparation(s)

  - **Essential oil:**

Monoterpenes, sesquiterpenes, diterpenes esters, and alcohols as main components α-cadinene, δ-cadinene, viridiflorol, bulnesol, ledol, α-copaene, β-selinene, cubenene, manoyloxide and 13-epi-manoyloxide (Demetzos *et al*., 1989; 1997).

In a study, the essential oil composition of *Cistus creticus* subspecies *corsicus* versus *eriocephalus* have been reported (Paolini *et al*., 2009) where, it appears that *C. creticus* subsp. *eriocephalus* and *C. creticus* subsp. *corsicus* from the Corsican–Sardinian continuum were differentiated by botanical characteristics (absence or presence of glandular trichomes) linked with essential oil production and composition of the volatile fraction (limonene or 13-epi-manoyl oxide, respectively, as the major component). It has been also affirmed that some differences are evident between the chemical profile of polyphenols in the *C. creticus* subsp. *creticus* and the other two subspecies; however, it appears to be clear that the secondary metabolites are similarly comparable (quantitative than qualitative differences) (Mastino *et al.* 2018).

  - **Water extracts from *Cistus***

In several studies performed from different populations from *Cistus creticus* (*C. incanus*) the polyphenolic composition of aqueous extracts (mostly infusion and decoctions) were searched. Three main groups of compounds were found, i.e. ellagitannins, flavonoids and phenolic acids derivatives. In the aqueous extract of *C. creticus* (*C. incanus*) isorhamnetin-O-rutinoside; rutin; (-)-(epi)catechin; (-)-(epi)gallocatechin; quercitrin; (-)-(epi)catechin-(epi)gallocatechin dimer; (-)-(epi)gallocatechin-(epi)gallocatechin dimer; quercetin-3- O-rutinoside-7-O-hexoside, quercetin-3- O-(2'-caffeoyl)-rutinoside; and myricitrin were identified as the most abundant compounds (Barrajón-Catalán *et al*., 2011), while in another study 29 polyphenols, including ellagitannins, flavanols, and glycosylated flavonols, were identified (Wittpahl *et al*., 2015).

Due to the rising consumption of *Cistus creticus* as infusions/decoctions, its herbal teas were examined several times and the results were compared with the results from other types of popular in the market teas compared (such as *Camellia sinensis*, Hoan Ngoc herbal tea and Rooibos infusions). *Camellia sinensis* infusions contained more catechins (1.56–82.65 mg/g) than *Cistus* (1.02–2.73 mg/g) but there was no catechin-3-gallate in any *Camellia* infusions. Caffeine, theobromine and theophylline were found practically only in *Camellia sinensis* (6.22–14.19 mg/g) and Vietnamese herbal tea (2.97 mg/g) while trigonelline was found at higher concentrations in both *C. incanus* (*C creticus*) (6.29–14.34 μg/g) and Rooibos infusions (10.54–14.29 μg/g). (Jeszka-Skowron et al. 2018). In order to validate the polyphenolic content and composition of currently available commercial products, 15 trade samples of coarse-cut *Cistus* plant material from different trademarks, pharmacies and health retailers

were included in an analytical investigation. Twelve of these trade samples were originally labeled as *C. incanus* and one as *C. creticus*, and two further *Cistus* herbal "teas" had no species designation on the label. The content of water-soluble compounds of the trade samples varied highly, from nearly zero to high percentages depending on the plant material and the geographic area of origin. It appeared also that extracts of *C. creticus* were usually characterized by punicalagin as the main compound and punicalagin gallate (Lukas et al. 2022; Bernacka *et al.* 2022).

In another study the total phenolic content (TPC) of a water extract of *Cistus creticus* (*C. incanus ssp creticus*) (1g / ml of water) was evaluated, resulting to 14.8%. The results were expressed in gallic acid equivalents (GAE), i.e., mg GAE/g DW (DW: Dry Weight of herb) (Ziagova *et al.* 2022).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

1.2. Search and assessment methodology

Search engines used: public databases (google, yahoo); key word: "*Cistus creticus* /cretici" or "*Cistus incanus*/incani" and "tea" or "extract", November 2022

Scientific databases: Scifinder, Scopus; key words: "*Cistus creticus* /cretici" or "*Cistus incanus*/incani" and "tea" or "extract", November 2022.

Medical databases: Pubmed, Cochrane library; key words: "Cistus creticus/cretici" or "Cistus incanus/incani" and "tea" or "extract", November 2022.

Toxicological databases: Toxnet; key words: "Cistus incanus/incani" or "Cistus creticus/cretici" and "tea"or "extract", November 2022

Pharmacovigilance resources: Eudravigilance, Vigibase, Date, Key words: "*Cistus creticus* /cretici" or "*Cistus incanus*/incani" and "tea" or "extract" (March 2023)

Data from EU and non-EU regulatory authorities: EU market overview

Other resources: Library of the National and Kapodistrian University of Athens (Pharmacy and Pharmacognosy library).

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

The request for information exchange concerning preparations from "Cistus creticus/cretici" revealed that there are no medicinal products marketed in the EU/EEA containing preparations from *Cistus creticus* as single active substance.

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Regulatory Status (date, Member State, Type of Marketing authorisation/registration where possible)**
Dry extract from **Cisti incani herba** (4-9:1), extraction solvent: water	Traditional herbal medicinal product as demulcent for the symptomatic treatment of oral or pharyngeal irritations.	Compressed lozenge *Adults and adolescents over 12 years of age:* 1-2 compressed lozenges every 3 hours SD 76.8 – 153.6 mg DD 460.8 - 921.6 mg *[calculation based on SD 6 times a day]* If the symptoms worsen or no improvement occurs within 1 week, a doctor should be consulted.	19.05.2015, DE, TUR

Information on relevant combination medicinal products marketed in the EU/EEA

No data.

Information on other products marketed in the EU/EEA (where relevant)

The request for information exchange concerning preparations from *Cistus creticus*, herb revealed that the comminuted herbal substance is widely distributed in both the food and cosmetics sectors all over Mediterranean countries, while *Cistus* x *incanus* L. is listed in the "Inventory List of Herbals considered as Food" by the European Herbal Infusion Association (EHIA) (EHIA, 2013).

A private German database for natural remedies "Grüne Liste" (Präparateliste Naturheilkunde, 1998)contains a special branded extract CYSTUS052 from a distinct variety of *C. incanus*, with a content of more than 26% of polyphenol which does not fall into the scope of the present monograph.

Despite its long traditional use in some South European countries, *Cistus* is subject to the "novel food regulation" (European Commission, 2015) (Lukas *et al*. 2021).

This plant variety is the main ingredient for several final commercial products (Cream, tea, syrup, bio pastilles, decoction, food supplements etc) which do not fall into the scope of this monograph (Zalegh *et al*. 2021).

In Belgium, according to the Royal Decree of 1997 (updated in 2017), *Cistus creticus* (fructus, folium and resina) can be used in food supplements without any restriction as condition of consumers (age, pregnancy, lactation), posology and duration of use is concerned.

Also in Poland, several products are on a list of the notified food: 8 herbs, dried herbs or dried herbs in form of sachets declared to contain *Cistus incanus* L.; 1 product in a form of tablets of powdered/comminuted *C. incanus* herb; 2 products in a form of liquid extracts of *C. incanus* herb; 1 product containing dried herb of *Cistus creticus*; 1 capsules containing dried herb of *C. creticus*; 1 product in form of drops containingcombination of *Cistus incanus* L and *C. ladanifer* L. ; 1 liquid, 1 capsules and 1 dried herb declared to be Cistus, unidentified species.

2.1.2. Information on products on the market outside the EU/EEA

In Switzerland there are lozenges (since Nov 2009) containing Cistus extracts marketed as medical devices. One lozenge contains 73.5 mg *Cistus villosus* (syn= *Cistus creticus* subsp *eriocephalus*) extract (no further information provided).

2.2. Information on documented medicinal use and historical data from literature

Historically, the plant saw extensive use in Minoan Crete society, later Herodotus mentioned it in his book "The Histories" how the Arabs obtained the aromatic "Ladanon resin" from the beard of goats that grazed on the plant. Later, Hippocrates named the plant "Cistus (from the Greek: Κίστος) and praised its valuable resin. In the Roman era, Celsus describes the use of "Ladanon" in plasters for the treatment of malignant dermal diseases. Dioscorides mentioned in "*De Materia Medica*" that the plant had been used for over 2000 years until his era. Overall, the plant has been used traditionally by many nations as an antimicrobial, antifungal, expectorant and for its anti-inflammatory effects such as the treatment of stomach ulcers. The resin (ladano) and leaves of *Cistus creticus* known since antiquity, during the Middle Ages, served for incense uses because of its pleasant fragrance. It is/was also used as an expectorant against catarrh, externally for plasters to treat ulcerating wounds and as an ingredient for wound ointments. *C. creticus (C. incanus subsp. creticus)* L., was used as a laxative (depurativum) in the treatment of leprous diseases. Nowadays the plant is still being traditionally used in Cretan area as a herbal tea for combatting flu and coughThe highly aromatic gum or resin, called *ladanum* or *labdanum*, (*ladanum* and *labdanum* should not be confused with "laudanum" the name for an opium-based patent medicine popular in the United States in the 19th century) has been used in incenses since ancient times and remains among ingrediens of perfumes (www.mecklenburghsquaregarden.org.uk, Lukas *et al*. 2021, Zalegh *et al.* 2021, Tomou *et al*. 2022, Papaefthimiou *et al*., 2014).

The laxative effect is well known in Turkey; as 5% infusion the leaves of *C. creticus* L. and *C. salviifolius* L. are served against digestive trouble (Petereit *et al*., 1991), while traditionally also *Cistus cretici* tea was drunken in cases of bronchitis or colds in Cyprus (Lardos, 2006; Lardos *et al*., 2011).

According to Greek literature, the medicinal uses of herbal tea from the aerial parts of *Cistus creticus* with certain indications and posologies have been described in books (Gennadios, 1914; Fragaki, 1969; Anassis 1976; Spyrou, 1984).

In the island of Crete it is a popular folk medicine, used as herbal tea internally against gastrointestinal disorders, and cough associated with cold and externally for skin protective properties.

Moreover, aerial part preparations of *Cistus creticus* L. are traditionally used in Anatolia as a haemostatic agent (Karadağ *et al*. 2020).

The leaves of *Cistus* × *incanus* L. (pink rock-rose) are used generally as plant material rich in antioxidants by the food industry (Barrajón-Catalán *et al.* 2016).

Cistus incanus L. (CI) has been proposed as an innovative functional supplement of food products, added in bread from white wheat flour supplemented with the addition of 1%, 2%, 3%, 4%, and 5% of ground CI. Supplementation of bread with 3% CI produced a product with desirable characteristics which was also favored by consumers (Cacak-Pietrzak *et al*. 2019). Moreover, common wheat pasta (with a spaghetti shape) fortified with dried *Cistus incanus* in amount from 1 to 3% in wheat flour has been also proposed, in order to increase total phenolics content and antioxidant activity (Lisiecka *et al*. 2019). Moreover, it has been suggested the use of *cistus creticus* extract as natural and safe antioxidant, on lipid oxidation and shelf life of ready-to-eat beef cocktail sausages (Pamuk *et al*. 2022).

Table 2: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Reference**
Dried aerial parts of *Cistus creticus*	treatment of pneumonia and bronchial catarrh	Decoction of 10 g in 200 ml of water to boil till to remain the half (100 ml) [30 g in 600 ml] Single dose 10 g Daily dose 10-30g	Spyrou, 1984: Anassis 1976

2.3. Overall conclusions on medicinal use

According to the literature available the requirements for the period of medicinal use according to Directive 2001/83/EC as amended with respect to "traditional use" regarded fulfilled for the indications.

Oral use
Traditional herbal medicinal product for relief of cough associated with cold.

Based on available literature references the following posology is proposed:

Indications 1)

Adults and elderly

Decoction of 10 g in 200 ml of water to boil till to remain the half (100 ml) (appr. 20 min) (Spyrou 1984, Anassis 1976).
The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use.

The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

Table 3: Overview of evidence on period of medicinal use

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
Comminuted herbal substance	cough and cold	As a decoction of 10 g in 200 ml of water to boil till to remain the half	Spyrou 1984, Anassis 1976,

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		(100 ml) (approx. 20 min) 1- 3 times daily Daily dose:10-30 g	

3. Non-Clinical Data

Anti-inflammatory activity

In vitro:
Short-boiled aqueous extract ("not further specified") from leaves of *C. creticus* dose dependently inhibited the enzymatic activities of both alanyl aminopeptidase and dipeptidylpeptidase IV (Lendeckel *et al*., 2002). This inhibition was not reversible and very likely resulted from a covalent binding of reactive compounds to the enzymes.

The anti-inflammatory activity of extracts of *Cistus incanus* (probably *ssp. tauricus*) was tested *in vitro* in the chick embryo chorioallantoic membrane test (Petereit *et al*., 1991). An aqueous extract (prepared boiled with water for 5 min) ("not further specified") showed dose-dependent activity, which, however, was lower than that of the same extract after it was shaken with ethyl acetate; the activity of that ethyl acetate fraction was comparable with that of indomethacin and higher than that of sodium salicylate.

Cistus x incanus L. leaves ("not further specified") have been investigated for its anti-inflammatory effects (of an ethyl acetate fraction (EAF) on lipopolysaccharide (LPS) activated RAW 264.7 macrophages. HPLC analysis revealed myricetin and quercetin derivatives to be the major compounds in EAF; EAF up to 1 μM of total phenolic content, was not cytotoxic and inhibited the mRNA expression of interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) ($p < 0.05$) and the production of prostaglandins E2 (PGE2) ($p < 0.05$). Meanwhile, EAF triggered the mRNA expression of interleukin-10 (IL-10) and elicited the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), as well as the expression of its main target gene, heme oxygenase-1 (HO-1) ($p < 0.05$). These data indicated that EAF attenuates experimental inflammation via the inhibition of proinflammatory mediators and at least in part, by the activation of Nrf2/HO-1 pathway. These effects are likely due to myricetin and quercetin derivatives but the role of other, less abundant components cannot be excluded. (D' Ambrosio *et al.* 2020).

In vivo:
The anti-inflammatory activity of extracts of *Cistus incanus* (probably *ssp. tauricus*) was tested *in vivo* in rats with dextran induced paw oedema (Petereit *et al*., 1991). The activity of an aqueous extract of the plant boiled for 30 min, or a cold-water extract ("not further specified") or the ethyl acetate fraction prepared from an aqueous extract (boiled with water for 5 min) was compared with that of various concentrations of sodium salicylate in the rat paw oedema test. All the extracts showed little or no activity (Petereit *et al*., 1991).

Water extract (DER not further specified) and higher oligomeric proanthocyanidin fractions of *C. incanus* significantly inhibited TPA-induced oedema when applied topically at doses of 0.5 and 1 mg/ear in mice. Furthermore, the extracts and the two new pure compounds (gallocatechin-(4α→6)-gallocatechin-(4α→8)- gallocatechin, and epigallocatechin-3-O-gallate- (4ß→8)-epigallocatechin-3-O-gallate-(4ß→→8)-gallocatechin inhibited COX-1 and COX-2 activities. In addition, compound 2 exhibited an $IC_{50}$of 4.5 μM against COX-2 indicating its high selectivity towards COX-2 (Mansoor et al. 2016).

Antibacterial and antifungal activity

In vitro:
Bouamama *et al*. examined the antimicrobial activity of leaf extracts (not further specified) obtained *Cistus villosus* L. (= *incanus*) and *Cistus monspeliensis* L. against five strains of bacteria and five strains of fungi. All extracts showed inhibitory activity against microorganisms. In consecutive experiments the antimicrobial properties against microorganisms, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans, Candida krusei, Candida glabrata* and *Aspergillus fumigates* were investigated. Results showed that the different extracts differed clearly in their antimicrobial activities: *Cistus villosus* extracts exhibited stronger activity than *Cistus monspeliensis* extracts when used on *Staphylococcus aureus* (MIC=0.78 mg/ml) and *Candida glabrata* (MIC=0.19 mg/ml), which are the most susceptible microorganisms (Bouamama *et al*., 2006).

revealed that a *C. creticus* (syn *C. incanus*) infusion (an infusion of sample with 1 g of dried herb brewed with 100 mL boiling water and infused for 7 min (pH = 4.7). The polyphenols from four different commercial *C. incanus* herbal teas were extracted by standardized accelerated solvent extraction with Methanol 50% (V/V) for in vitro tests and by an infusion with water for in situ tests. Furthermore, the in vitro antibacterial activity of the *C. incanus* methanolic extracts against *Streptococcus mutans*, was examined using a live/dead assay (BacLight). With this approach, *C. incanus* yielded cariogenic properties using a live/dead assay (BacLight). Antibacterial studies of the essential oil of the leaves of *Cistus creticus and specifically subsp. eriocephalus* (Viv.) Greuter and Burdet were carried out in vitro against Gram-positive, Gram-negative organisms and fungi: *B cereus*, *B subtilis, C albicans, S faecalis, S aureus, S epidermidis, P aeruginosa* and *E coli.* Gram-negative bacteria (*P aeruginosa, E coli*) were more resistant than the Gram-positive bacteria (*B cereus, B subtilis, S faecalis, S aureus, S epidermidis*) and the yeast (*Candida albicans*) (Wittpahl *et al.* 2015).

The antimicrobial and antifungal activity of seven labdane-type diterpenoids isolated from the leaves of *Cistus incanus subsp. creticus* were assessed in vitro (Chinou *et al*., 1994). Antimicrobial effects were observed against S*. aureus, P. aeruginosae, K. pneumoniae,* antifungal effects against *C. albicans*.

Studies, which support the antimicrobial effects of studied cistus cretica plant against multiple types of bacteria are Barrajón-Catalán *et al.* 2011; 2016; Haouat *et al.* 2013.

Aqueous extracts of *C. incanus* (*C creticus*) (dried powder of aerial parts) of *C. incanus* (1.00 g) was mixed with 100 mL of boiling, de-ionised water. The infusions were brewed under cover and after 15 min filtered and then lyophilized, weighed and used for MIC tests. They revealed antibacterial activities more effective against Gram-positive bacteria, particularly *S. aureus* (MIC values from 0.5 to 32 mg/mL) and *S. epidermidis* (MIC values from 0.25 to 8 mg/mL) than Gram-negative bacteria. They were also weak inhibitors of *C. albicans* and *C. glabrata* growth (MIC values over 8 mg/mL) (Viapiana *et al.* 2017).

The antibacterial activity of the phenolics derived from fourteen *C. incanus* (*C creticus*) samples of different origin (Turkey, Albania, Greece, and an unknown geographical location) obtained as herbal teas from a local market of diet supplements. Their activities were assessed with the use of thin-layer chromatography–direct bioautography (TLC-DB) applied to crude extracts against the Gram negative naturally luminescent marine bacterium *Aliivibrio fischeri* and the Gram positive (+) soil bacterium *Bacillus subtilis* as the test microorganisms. Showing closely comparable and more strongly pronounced against the Gram positive than Gram negative bacterium. Crude extract containing flavonoid aglycons, free phenolic acids, non-polar flavonoid glycosides, polar flavonoid glycosides, and phenolic acids obtained through the acidic and basic hydrolysis from the respective glycosides. (Szeremeta et al. 2018). The same study went on studying the antibacterial components of different fractions derived from eleven commercial *C. incanus* (*C creticus*) herbal teas, then examined in the same way ((TLC-DB) using again *B. subtilis* and *A. fischeri* strains. Results proved apigenin, kaempferide and acylated kaempferol glycosides (cis- and trans-tiliroside and their conjugates with p-coumaric acid) to be antibacterial components.

The essential oil from the *Cistus* leaves of Tafraout, Morocco was obtained by hydro-distillation and after being analyzed (by GC-MS) the antibacterial properties of crude extract, fractions (flavonoids, tannins, saponins, alkaloids) and essential oil of *Cistus creticus* leaves were studied. The crude extract

and essential oil were examined for their antimicrobial and antifungal activities The *C. creticus* essential oil revealed a low efficacy against bacteria (MIC 1/8–1/32 v/v). The ethanolic extract tested was found to be limited to no activity against all bacteria tested except *Staphylococcus aureus*, which was inhibited from the first concentration (1.25 mg/mL). (Ait Lahcen *et al.* 2020).

Extracts from dried pulverized leaves of *Cistus creticus* (macerated at room temperature in hexane and ethyl acetate), volatile oil fraction obtained by steam distillation, as well as Cistus leaves extracted by boiling water for 30 min ("not further specified") according traditional and commercial use were assayed for their antibacterial activity against *Borrelia burgdorferi* sensu stricto (Bbss) *in vitro* using the antibiotic amoxicilline as standard and polysorbate 80 as solubilizer for lipophilic extracts (Rauwald *et al.* 2010; 2019). Comparison of the four plant preparations showed that the volatile oil exerted the strongest growth inhibitory effect. Even concentrations of 0.02% (w/v) volatile oil in cultivation media reduced the total number of bacteria to 2% in comparison to a growth control after an eight-day cultivation period. While the aqueous extract did not reduce bacterial growth, incubation with hexane and ethyl acetate extracts clearly inhibited microbial growth. The main volatile components were analyzed by GC-MS. The number of different labdane-type diterpenes as well as the total relative amount of diterpenes in the samples tested was highest in the essential oil of *C. creticus*. Manoyl oxide, 13-epi-manoyl oxide, 3-acetoxy-manoyl oxide and the monoterpene carvacrol were determined to be major constituents, accompanied by minor amounts of 3-hydroxy-manoyl oxide, all of which are known to exert antimicrobial activity.
Furthermore, the antimicrobial effects of 12 commonly used botanical medicines for their potential anti-*Borrelia burgdorferi* activity have been investigated *in vitro*. Among them, 7 natural product extracts at 1% were found to have good activity against the stationary phase *B. burgdorferi* culture compared to the control antibiotics \ among which was also *C. incanus* (*C. creticus*), showing MIC (%) 0.25–0.5% in comparison with 5 µg/ml Doxycycline 0.25 µg/mL, 5 µg/ml Cefuroxime 0.13 µg/mL. (Feng et al. 2020).

Antiviral Activity

In vitro:
A plant extract from a special variety of *Cistus incanus* rich in polyphenols (CYSTUS052, extracted with ethanol 20%), exhibited antiviral activity against the avian influenza A virus (H7N7) in cell (Droebner *et al*., 2007). In MDCK cells, a 90% reduction of plaque numbers on cells pre-incubated with the plant extract was achieved. The same extract was demonstrated to exert an anti-influenza virus activity in A549 or MDCK cell cultures infected with prototype avian and human influenza strains of different subtypes (Ehrhardt *et al*., 2007). A special branded extract (CYSTUS052 with polyphenols approx. 26%) treatment resulted in a reduction of progeny virus titres of up to two logs. At the effective dose of 50 µg/ml the extract did not exhibit apparent harming effects on cell viability, metabolism or proliferation. Viruses did not develop resistance to the extract when compared to amantadine that resulted in the generation of resistant variants after only a few passages. The authors suggested that the effect appears to be mainly due to binding of the polymeric polyphenol components of the extract to the virus surface, thereby inhibiting binding of the haemagglutinin to cellular receptors.

Cistus creticus (Ci) extract inhibited clinical HIV-1 and HIV-2 isolates, *in vitro* and, importantly, a virus isolated with multiple drug resistances, showing anti-HIV activity. Antiviral activity was selective for virus particles, preventing primary attachment of the virus to the cell surface and viral envelope proteins from binding to heparin. Bioassay-guided fractionation indicated that Ci extract contains numerous antiviral compounds and therefore has favorably low propensity to induce virus resistance. Indeed, no resistant viruses emerged during 24 weeks of continuous propagation of the virus in the presence of Ci extracts. Finally, Ci extracts also inhibited infection by virus particles pseudotyped with Ebola and Marburg virus envelope proteins, indicating that antiviral activity of Ci extract extends to emerging viral pathogens. (Rebensburg *et al.* 2016).

Several extracts and fractions of labdanum - standardised on labdane-type diterpenes via GC-MS - on their activity against the dengue virus (DENV-2 strain 00st-22A) were tested in *in vitro* Vero cell cultures (96-well-plates, 5 days). Preliminary experiments with a labdanum diethyl ether raw-extract

did not yield measurable results due to cytotoxic effects against Vero cells. In all following experiments, cell viability was constantly checked using the MTT-test. Fractionation of this raw-extract by liquid-liquid-extraction and column-chromatography on silica-gel (gradient elution with hexane, EtOAc, $CHCl_3$, MeOH) succeeded in separating the anti-viral activity of labdanum from its cytotoxic effect. In the most active fraction GS5 at 30 µg/ml, dengue virus proliferation was 100% suppressed and cell viability was over 90%. Structural elucidation of major constituents of GS5 is currently ongoing, but thin-layer chromatography showed that this fraction is mainly dominated by manoyl-oxides, a class of labdane-type diterpenes with known antimicrobial activity. Claims concerning the antiviral activity of above ground parts of *C. creticus* have been made previously, but these generally ascribe this activity to hot water soluble polyphenols and propose an unspecific tanning effect of the viral surface proteins as the mechanism of action. However, the water-soluble fraction enhanced viral proliferation. (Kuchta *et al.* 2020).

In vivo:
A special branded extract (CYSTUS052, polyphenolic content >26%.) in the form of aerosol subjected as treatment of mice infected with a mouse-adapted highly pathogenic avian influenza virus (FPV, H7 N7) protected the animals against clinical disease symptoms. Inbred female Balb/c and C57Bl/6 mice at the age of 6–8 weeks were used. Treatment of mice was performed in inhalation chambers for 5 days. Either five mice were treated at the same time in an inhalation chamber or single mice were treated in an inhalation tube. From the reported data, it was proposed a potential mechanism of action, where polyphenolic ingredients of the branded extract blocked virus infection by a direct (physical) interaction with the virus particles (Droebner *et al*., 2007).

In several review articles data have been collected on potential preventive and therapeutic health benefits of Complementary and Integrative Medicine (CIM) that might be useful during the COVID-19 pandemic. In several among them, the safe and supportive use of *Cistus creticus* herbal teas has been suggested (Şener 2020, Saifulazmi *et al.* 2022).

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

Table 3: Overview of the main non-clinical data/conclusions of *Cistus creticus*

Herbal preparation tested **comparable/similar preparations to preparations of the monograph**	**Strength** **Dosage** **Route of administration**	**Experimental model** **In vivo/ In vitro**	**Reference** **Year of publication**	**Main non-clinical conclusions**
comparable/similar preparations to preparations of the monograph				
Aqueous extracts of *C. incanus* (*C creticus*)	???	*In vitro* activity Panel of Gram + and Gram – bacteria	Viapiana et al., 2017	effective against Gram-positive bacteria, particularly *S. aureus* (MIC values 0.5 - 32 mg/mL) and *S. epidermidis* (MIC 0.25 - 8 mg/mL)
lyophilized aqueous extracts from *Cistus creticus*	0.25 and 0.50 g/kg *p.o*.	*In vivo in fasted male rats* Antiulcer activity	Attaguile *et al*., 1995	significant dose-related protective effects (18 and 30 % inhibition respectively)

Herbal preparation tested **comparable/similar preparations to preparations of the monograph**	**Strength** **Dosage** **Route of administration**	**Experimental model** **In vivo/** **In vitro**	**Reference** **Year of publication**	**Main non-clinical conclusions**
		(induced with ethanol, indomethacin reserpine and serotonin)		
Water extract of *C. incanus*	Topical application of 0.5 and 1 mg/ear	*in vivo* in mice ant-inflammatory activity (selectivity towards COX-2)	Mansoor et al., 2016	Inhibition of PA-induced oedema, while they inhibited COX-1 and COX-2 activities
other preparations				
Cistus creticus methanol extract, essential oil and pure labdane-type diterpenoids were assayed	Several doses	*in vitro* Antimicrobial activity against Gram-positive and Gram-negative bacteria; dilutions (1/1600)	Chinou. et al., 1994	Antimicrobial effects observed against S*. aureus, P. aeruginosae, K. pneumoniae,*
leaf extracts of *C. creticus* (not further specified)	Several doses (?)	*in vitro* antimicrobial activity against five strains of bacteria	Bouamama *et al*., 1999	all extracts showed antimicrobial activities: *especially against S aureus* (MIC=0.78mg/ml)
C. incanus extract (ethanol 20%, with a polyphenolic content > 26%)	ED 50 µg/ml	*in vitro* Antiviral Activity against H5N1	Ehrhardt *et al*., 2007	antiviral activity against influenza A virus (H7N7) in cell model
C. incanus extract (ethanol 20%, with a polyphenolic content > 26%)	1 mg/ml Inhalation (5 days in inhalation chambers)	*in vivo* in mice Antiviral Activity of H7N7	Droebner *et al*., 2007	pre-treated mice: no development of disease, no differences in their body temperature, no differences in their gross motor-activity, no exhibition of histological alterations of the bronchiolus epithelial cells
Single substances				

Herbal preparation tested comparable/similar preparations to preparations of the monograph	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
higher oligomeric proanthocyanidin fractions of *C. incanus* gallocatechin-(4α→6)-gallocatechin-(4α→8)- gallocatechin (compound 1) and epigallocatechin-3-O-gallate- (4ß→8)-epigallocatechin-3-O-gallate-(4ß→→8)-gallocatechin (compound 2)	Topical application of 0.5 and 1 mg/ear	*In vivo* in mice ant-inflammatory activity (selectivity towards COX-2)	Mansoor et al., 2016	Inhibition of PA-induced oedema 1 and 2 inhibited induced oedema while they inhibited COX-1 and COX-2 activities. Compound 2 IC50=4.5 μM against COX-2 (indicating its selectivity towards COX-2)

3.1.2. Secondary pharmacodynamics

Antioxidant activity

The effects of crude aqueous extracts from *Cistus incanus* and *Cistus monspeliensis* on DNA cleavage and their free-radical scavenging capacity were investigated (Attaguile et al., 2000). In addition, their effect on lipid peroxidation in rat liver microsomes was evaluated. These extracts showed a protective effect on DNA cleavage and a dose-dependent free radical scavenging capacity; *Cistus monspeliensis* was more active than *Cistus creticus*; these results were confirmed by a significant inhibition of lipid peroxidation in rat liver microsomes.

Studies carried out *in vitro* highlighted the plant's phenolic compounds' (extracted in water) ability to destroy model free oxygen radicals (Tomou *et al.* 2022, Ait Lahcen *et al.* 2020) and were further backed by more sophisticated laboratory methods (LC-online TEAC) (Riehle 2013). Another study showed how aqueous extracts of *Cistus* can reduce free radical damage to DNA models, induced by UV light (Attaguile *et al.* 2004).

The essential oil from the Cistus leaves of Tafraout, Morocco was studied. Total polyphenol, flavonoid, and condensed tannin's contents were determined using Folin-Ciocalteu, aluminum chloride and vanillin colorimetric methods, respectively. The antioxidant activity of essential oil and different extracts from cistus leaves was determined by two methods: free radical scavenging method DPPH and the FRAP) The different extracts studied showed an antioxidant activity, with 50% inhibition concentration (IC50) values varied between 0.01 and 2.53 mg/mL for DPPH test and 0.1 to 0.53 mg/mL for FRAP test. The antioxidant capacity was significantly higher for flavonoids and saponins, compared to the other extracts (Ait Lahcen *et al.* 2020, Lukas et al. 2021, Ziagova *et al.* 2022).

Cytotoxic activity

Seven labdane derivates isolated from the leaves of *Cistus incanus subsp. creticus* and characterised by GC/MS were observed to exert antiproliferative activity (IC_{50} values 0.035-10 μg/ml) against three tumour cell lines (KB. P388 and NSCLC-N6) (Chinou *et al*., 1994). Two [13E-labd-13-ene-8a,15 diol and 13E-labd-7,13-dienol out of nine labdane type derivatives isolated from the plant *Cistus incanus* subsp. *creticus* and from its resin "Ladano" were found to show cytotoxic activity against human leukemic cell lines (IC_{50} 25 -50 μg/ml)(Dimas *et al*., 1998).

Aqueous extracts of *Cistus incanus* L. and *Cistus monspeliensis* L. exerted cytotoxic and growth inhibitory effects on normal human prostate cells (PZ-HPV-7 and PNTIA) and on a lung fibroblast cell line (V79-4) (Vitali *et al*., 2011).

An ethanolic extract from *Cistus creticus* (ethanol 20%, no further information) with a content of more than 26% polyphenols was tested in "Madine Darby" canine kidney cells at concentrations from 2 to 50 µg/ml. After three days of incubation with the maximum concentration of 50 µg/ml, approx. 92% vital cells were counted compared to approx. 97% in the control. The difference was not statistically significant. The tested Cistus extract did not interfere negatively with the proliferative and metabolic capacity of cells as determined in the MTT assay. (Ehrhardt *et al*., 2007).

Validity behind the traditional use of *C. creticus* against cancer cells was recently revealed while extracts rich in diterpenes showed *in vitro* efficacy against breast, melanoma and cervix cancer cell lines (Skorić *et al.* 2012). Although the plant's extracts demonstrated adequate cancer cell inhibition, healthy human cells were not affected in these studies, hinting at a good safety profile (Moreira *et al*. 2017).

Moreover, cytotoxic assay was performed for the crude *C. incanus* (*C creticus*) extracts against the human colon adenocarcinoma cells and a moderate yet well measurable cytotoxic effect was observed with all investigated *C. incanus* samples. In analogy to antibacterial activity, also in this case cytotoxic potential of all investigated crude *C. incanus* extracts was similar (Szeremeta *et al.* 2018).

Antiulcer activity

In vivo:
The potential protective effect of short-boiled aqueous extract of *Cistus incanus* ("not further specified") in 36 hr fasted male rats was evaluated (Attaguile *et al*., 1995). Gastric lesions were induced with absolute ethanol (1 ml, p.o.), 1 N HCl (1 ml, p.o.), indomethacin (15 mg/kg, i.p.), reserpine (20 mg/kg, i.p.) and serotonin (25 mg/kg, s.c.). The extract, containing bioflavonoids, was orally administered in the range from 0.25 to 0.50 g/kg. The aqueous extract demonstrated antiulcer activity in all of the abovementioned models and was found to have significant dose-related protective effects in all these experimental models, plus was effective against reserpine- and serotonin-induced mucosal congestion and haemorrhagic ulcers (Attaguile *et al.*, 1995).

Spasmolytic activity

Ex vivo:
The lyophilized aqueous extracts from *Cistus creticus* L. and *Cistus monspeliensis* L. were evaluated for myorelaxant activity by using isolated smooth muscle of rat ileum and rat aorta (Attaguile *et al*., 2004). Both extracts concentration-dependently inhibited the contractile response to acetylcholine (ACh), phenylephrine (PE) and to 100 mM KCl., evidence leads to the speculation that these effects are brought about by the extracts' phenolic compounds and specifically flavonoids, since such secondary metabolites are known to cause muscle relaxation.

***In vivo* haemostatic properties**

The air-dried aerial parts of *C. creticus* , were extracted with methanol "not further specified". Gels were prepared, followed by the haemostatic activity evaluation using Wistar albino rats in vivo tail tip amputation model. The chemical characterization of the total extract was performed by high-performance thin-layer chromatography (HPTLC). The methanol extract was loaded to a hydrogel base to complete a concentration of 2.5 and 7.5%. As a result, the 2.5% extract gel was found more effective on both bleeding time and amount. Hyperoside and tiliroside, which may be the components responsible for the haemostatic properties of the analyzed plant material, were dereplicated as major constituents (Karadağ *et al.* 2020).

3.1.3. Safety pharmacology

No data available

3.1.4. Pharmacodynamic interactions

None reported.

3.1.5. Conclusions

Cistus creticus L., endemic Mediterranean species was used as healing herbal tea and consumption has been described mainly traditionally for the relief of upper respiratory disorders (cough associated with cold).
Even though the published data referring to the exact proposed indications and preparations are limited, the scientific data on the mentioned pharmacological activities do not contradict the plausibility of the proposed indications for traditional uses.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data available

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

No data available for the decoction described in the monograph.

Within the call for data unpublished data for an aqueous extract of *C. creticus /incanus* herba (containing at least 20% polyphenols, no further information available) were provided by interested parties concerning single dose toxicity, sub-chronic toxicity and genotoxicity.

3.3.1. Single dose toxicity

The polyphenol-rich aqueous extract was applied orally in Sprague Dawley rats; cut-off value was 5000 mg/kg body weight In house data acute oral toxicity with Extr. Cisti e herb. aquos. sicc. > 20% total polyphenols in Sprague Dawley rats. 2009.

3.3.2. Repeat dose toxicity

In order to investigate repeat-dose toxicity a 28-day study in rats with the polyphenol-rich aqueous extract followed by a 14-day recovery period was performed by daily gavage. The test item was administered to the animals at the dose levels of 0, 100, 500 and 1000 mg/kg body weight. From the control and highest dosage groups animals were used to study reversibility or delayed occurrence of symptoms, if any. No statistically significant effects were observed in both male and female animals of all study groups during the treatment and reversal period. Within the setting of this study, the NOAEL level was determined to be at least1000 mg/kg bw (In house data 28-DAY-TOXICITY-STUDY. Repeated dose 28-day oral toxicity study with Extr. Cisti e herb. aquos. sicc. > 20% total polyphenols by daily gavage in the rat followed by a 14 day recovery period. 2010; In house repeated dose 28-day oral toxicity study with extr cisti herb aquos sicc min 20% total polyphenols BY Dby daily gavage in the rat followed by a 14 day recovery period 2010.

3.3.3. Genotoxicity

The polyphenol-rich aqueous extract of Cistus herba were examined in different tests.

For the Ames tests 5 *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 (with and without S9, with and without pre-incubation), for the *in vitro*-mammalian cell gene mutation

assay (mouse lymphoma thymidine kinase locus) the cell line L5178Y, and for the evaluation of the micronucleus test immature erythrocytes of the mouse were used.

The aqueous extract was assessed to be non-mutagenic in the bacterial reverse mutation assay (In house data AMES-TEST. Reverse Mutation assay using bacteria (*Salmonella typhimurium*) with *cystus incani* (PC-2007-155) 2007, In house data AMES-TEST. Reverse mutation assay using bacteria (*Salmonella typhimurium*) with Extr. Cisti e herb. aquos. sicc. 2009).

3.3.4. Carcinogenicity

No data are available.

3.3.5. Reproductive and developmental toxicity

No data are available.

3.3.6. Local tolerance

No data are available.

3.3.7. Other special studies

No data are available.

3.3.8. Conclusions

No studies have been published concerning the toxicological properties of the preparation of *Cistus creticus* described in the monograph. Data on genotoxicity testing provided for a polyphenol-rich extract cannot be transferred to the preparation described in the monograph. From experiments (not published), it appears that there is already a substantial difference between the polyphenolic content of decoction and infusion (9.5% and 2% respectively), while the data provided refer to a preparation containing even higher amounts of polyphenols (20%). At least the increased content of polyphenols reflect a different composition of the preparations. Therefore, no data on genotoxicity are available for the preparation described in the monograph and a list entry cannot be supported.

3.4. Overall conclusions on non-clinical data

The reported pharmacological effects are not considered contradictory to the traditional uses for the relief of cough associated with cold as well as skin inflammation.
Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of decoctions of *Cistus creticus* are not available. Some data on genotoxicity conducted with special water extract (20% polyphenolic content) exist, however, their relevance for the traditional herbal preparations (decoction) was not shown.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

In situ experiments indicated that rinses with a *C. incanus* infusion reduced the initial bacterial colonization of enamel samples exposed to oral fluids for over eight hours. Furthermore, it was shown by transmission electron microscopy that the application of a *C. incanus* infusion modifies the ultrastructure of the acquired enamel pellicle, yielding a more electron-dense morphology. It can be assumed that the polyphenols are responsible for the observed effects (Wittpahl *et al*., 2015).

No clinical studies were performed with the preparation mentioned in the monograph. With an aqueous extract (no further information available or a special branded preparation) some clinical studies were performed. Since they were not taken into consideration for the monograph, they will be only shortly mentioned.

Clinical study on healthy subjects

A pilot study with 24 healthy volunteers was designed to determine if a 12-week administration of *Cistus incanus* (syn *C. creticus*) herbal tea, containing phenolic acids and flavonoids, reduces cardiovascular risk factors including oxidative stress and dyslipidaemia in healthy adults. Phenolic compounds profile and antibacterial activity of *Cistus incanus* (syn *C. creticus*) infusion were also measured. (Kuchta et al. 2021, Tomou *et al.* 2022).

Clinical studies in patients

The efficacy of a Cistus preparation from a special Cistus brand was tested in a small open controlled observational study of 53 patients (age 9-85 years) with painful inflammation of the throat (tonsillopharyngitis). On the first day after the onset of symptoms, the decoction was gargled with for two minutes every three hours and then swallowed. The next day (for one week), gargling was done 5 times a day for two minutes and then the decoction was swallowed again. The control group consisted of 18 patients (age 15-78 years) underwent the same procedure; only instead of Cystus decoction green tea was taken (Kiesewetter, 2002).

A small clinical study (Kalus *et al*., 2009) was performed, in which 160 patients (age 7–81 years), suffering from an infection of the upper respiratory tract by clinical signs, participated. The product

investigated (lozenges) consisted of the same special branded cistus extract. Only 129 patients completed the study, 82.5% of the *Cistus* group and 80.0% of the placebo group.

In another prospective, randomized, non-blinded open trial study (Kalus et al., 2010) 300 volunteers (age 5–85 years) suffering from an infection of the upper respiratory tract were recruited with the same special branded cistus extract as lozenge (6 times 2 lozenges daily).The subjects of the control group gargled and swallowed down 8 times 100 ml green tea on the first day of treatment, nd on the following 3 days 4 times daily 100 ml.

4.3. Clinical studies in special populations (e.g. elderly and children

In all existing clinical trials (Kiesewetter, 2002; Kalus *et al*., 2009; 2010) with a special branded Cistus extract, also children and adolescents have been participated. However, no special information on these groups were provided

4.4. Overall conclusions on clinical pharmacology and efficacy

No conclusions on clinical pharmacology and efficacy of the herbal preparation described in monograph can be drawn as the clinical trials (Kiesewetter 2002; Kalus *et al*., 2009; 2010) have been conducted with a special branded Cistus extract.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

From clinical studies performed with special herbal products () it can be concluded that the incidence of undesirable effects for Cistus is low.

There are no concrete data concerning patient exposure.

5.2. Patient exposure

There are data concerning patient exposure

5.3. Adverse events, serious adverse events and deaths

One case report on allergenicity of *Cistus creticus* has been reported (English & Cronin, 1988;).

A 53-years old housewife who developed dermatitis of the wrists and ankles which had begun and persisted during the summer months was reported (English & Cronin, 1988). She complained of a similar rash the previous summer, which had cleared in the winter. She was a keen gardener. She was patch tested with the ICDRG standard series of allergens and with 40 plants from her garden classified as irritant. She reacted to colophony and to several of the irritant plants. From the morphology of the positive patch tests it was not possible to deduce causality between the allergic reactions and the application of the plants. To elucidate which reactions were allergic, the patient performed open tests with each leaf in sequence. She was asked to rub the leaf on a delineated area of the flexor aspect of her forearm twice a day for 2 days. She has tested each leaf and responded only to *Cistus creticus.*

3 cases of not serious hypersensitivity were reported (Eudravigilance) after the consumption of *Cistus incanus* (*C. creticus*) herb (4-9:1) water extract, while from Vigibase overview were reported another two cases in male subjects, both in Morocco, after consumption of *Cistus creticus*, in parallel use the one with *Linum usitatissimum* and the second one with *Aristolochia fontanesii.*

Pharmacovigilance resources through Vigilyse as well as Eudravigilance from EMA were searched. No concerns arise from the few available data from case reports in the data bases up to 22 November 2022.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

For safety reasons the use and due to lack of adequate scientific and clinical data, in these populations the use is not recommended.

5.5.2. Contraindications

No data available.

5.5.3. Special warnings and precautions for use

Hypersensitivity to the active substance.

5.5.4. Drug interactions and other forms of interaction

Drug interactions from clinical trials or case studies have not been reported so far.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Adverse events serious adverse events and deaths have not been reported so far. Furthermore, drug interactions from clinical trials or case studies have not been reported so far. Thus, on its traditional use, pink rockrose herb shows not to be harmful in the specified conditions of use (recommended indications/recommended preparations).

6. Overall conclusions (benefit-risk assessment)

The comminuted herbal substance of dried herb from *Cistus creticus* have been used in traditional - medicine in the European Union, for more than 30 years. Based on the available data from literature sources the requirements for traditional use are regarded fulfilled for the comminuted herbal substance as herbal tea (decoction) for oral use.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC. It seems that analytical marker(s) are polyphenolic metabolites of the plant.

The data on safety/genotoxicity do not be considered sufficient to support a European Union list entry for the abovementioned herbal preparations and indications.

In the absence of available data, it is recommended not to use traditional herbal medicinal products containing *Cistus creticus* herbal tea during pregnancy and lactation.

The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use.

The use in children and adolescents under 18 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

So far, serious adverse events and deaths as well as drug interactions from clinical trials have not been reported. There are no safety concerns from the existing case reports in the Vigibase data bases up to November 2022. Adequate tests on reproductive toxicity, genotoxicity (according the herbal preparations proposed above) and carcinogenicity have not been performed.

Overall, the available preclinical, and toxicological evidence in more condensed extracts (higher polyphenolic content) demonstrated a safety profile for *Cistus creticus*. Therefore, *Cistus creticus* tea (decoction) is regarded also as safe.

Annex

List of references